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## Commentary

# Glucose–insulin–potassium infusion in sepsis and septic shock: no hard evidence yet

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## Abstract

There is no hard evidence yet for a positive effect of glucose–insulin–potassium infusion in sepsis, septic shock or burn patients. Each individual element of the glucose–insulin–potassium regimen, and eventually euglycaemia, should theoretically be beneficial. At present, evidence exists only for reduced mortality with strict metabolic treatment (i.e. blood glucose levels of 4.4–6.1 mmol/l) in critically ill patients admitted to surgical intensive care units, and for better metabolic regulation (i.e. blood glucose levels of 7.0–10.0 mmol/l) in patients with hyperglycaemia and/or diabetes mellitus, and in patients without signs of heart failure (i.e. Killip class I) during acute myocardial infarction.

**Keywords** euglycaemia, glucose, insulin, myocardial infarction, sepsis, septic shock

Recently, in this journal, Dr Undurti Das [1] suggested that treatment of sepsis, septic shock and burns should also include infusion of glucose–insulin–potassium (GIK), with the objective of the infusion being to achieve plasma glucose concentrations below 6.1 mmol/l (<110 mg/dl). That conclusion was based on the combined results of a number of studies. In our opinion, however, no single clinical trial has yet been reported that supports this conclusion.

## Euglycaemia in critically ill patients

It has been shown that achieving and maintaining euglycaemia (i.e. plasma glucose concentrations of 4.4–6.1 mmol/l) in patients admitted to surgical intensive care units leads to marked reductions in morbidity and mortality [2]. However, in that study the investigators did not use a GIK infusion; rather, meticulous regulation of serum glucose was achieved by combining intensive insulin treatment with intravenous glucose (200–300 g/24 hours). The following day the infusion was replaced by parenteral nutrition, combined parenteral and enteral nutrition, or enteral

nutrition, according to a set scheme. Potassium was only supplemented when a check-up showed that hypokalaemia was either imminent or present (G van den Berghe, ICC van der Horst, personal correspondence).

## Glucose–insulin–potassium infusion in sepsis, septic shock and burns patients

No studies are available in cases of sepsis, septic shock and burn patients in which euglycaemia was pursued with the aid of GIK infusion and that assessed mortality. There are few data pertaining to the haemodynamic effects of GIK in sepsis. In 15 patients with septic shock, GIK infusion led to an increase in cardiac output [3]. This effect was also shown in 14 patients with peritonitis and signs of hypovolaemic shock, in spite of positive fluid balance and catecholamine treatment [4]. In burns victims intravenous GIK had the same effect [5]. This appears to clarify the roles of the individual components of GIK, in particular with regard to haemodynamic support of the patient by insulin [6]. In the study conducted in a surgical intensive care unit [2], patients

with sepsis formed a small subgroup (maximum 5%). The fact that there were four times as many patients who died from established sepsis in the conventionally treated group as compared with the intensively treated group supports the value of intervention in glucose metabolism during sepsis. A problem that should be anticipated is obtaining and maintaining euglycaemia; after all, one of the features of sepsis is the presence of hyperglycaemia as well as hypoglycaemia. The scheme used in the above-mentioned study [2] has not been validated in septic patients. It is to be expected that serum glucose values will have to be checked more frequently than once every 2–4 hours.

### Metabolic treatment in acute myocardial infarction

Metabolic treatment during myocardial ischaemia has been studied before. The Diabetes Insulin Glucose Infusion Acute Myocardial Infarction (DIGAMI) study, which included 620 patients, is the only study that aimed at meticulous regulation of serum glucose concentrations by infusing glucose and insulin [7,8]. Patients with known diabetes mellitus or serum glucose concentrations greater than 11.0 mmol/l were randomly assigned to an insulin–glucose infusion for 24 hours, followed by a minimum of 3 months of intensive insulin therapy, or to conventional treatment. The objective was to maintain serum glucose concentrations between 7.0 and 10.0 mmol/l, which is well above concentration range of 4.4–6.1 mmol/l referred to above. After 1 year, those investigators found that, in particular, the group of patients who had had no previous insulin treatment and were not known to have risk factors such as a history of myocardial infarction gained most from the glucose metabolism intervention (mortality was 8.6% versus 18.0% in the control group). For the study population as a whole, the absolute reduction in mortality was 7.5% ( $P=0.0273$ ).

However, a definite place for GIK infusion in the treatment of acute myocardial infarction has not yet been settled. In 1997, a meta-analysis of studies of GIK in the treatment of acute myocardial infarction was published [9]. That meta-analysis included nine studies and 1932 patients, and showed that GIK treatment resulted in a reduction in 30-day mortality from 21% to 16.1% ( $P=0.004$ ). In the four studies in which GIK was administered at high doses ( $n=228$ ) the difference appeared to be even larger: a reduction from 12% to 6.5% (not significant). There were substantial differences between the nine studies, in particular with regard to the time at which the first symptoms appeared and the start of treatment, and regarding the composition of the GIK cocktail and the duration of treatment. Moreover, only 17 patients were treated by adding GIK to reperfusion, which is the present standard treatment.

The Estudios Cardiológicos Latinoamerica (ECLA) pilot trial [10], including 490 patients, showed that 30-day mortality in the group of patients randomly assigned to GIK was lower

than that in the control group (6.7% versus 11.5%; not significant). As mentioned in the commentary of Das [1], the effect was most pronounced in patients in whom GIK had been combined with reperfusion treatment, mostly thrombolysis (5.1% versus 15.1%;  $P=0.01$ ). However, mortality was very high in the control group, even higher than in the control group of patients who had not been treated with reperfusion (11.5%). Moreover, the Polish GIK (Pol-GIK) trial [11], which was published 1 year later, could not confirm the results of the ECLA pilot trial. In a group of 954 patients, the mortality of 8.9% in the GIK group was even significantly higher than that in the control group (4.8%;  $P=0.01$ ). Mortality due to a cardiovascular incident was not significantly different, and as such the cause of the difference remained obscure.

The guidelines of the American College of Cardiology/American Heart Association state that GIK in the treatment of acute myocardial infarction is very promising, but that it will take a large randomized study to determine its effectiveness once and for all [12].

Recently, the Glucose–Insulin–Potassium Study (GIPS) [13] reached its conclusion. In that study 940 patients were randomly assigned to primary coronary angioplasty with GIK (glucose 20% with 80 mmol potassium at a rate of 3 ml/kg body weight/hour and 50 IU insulin in 50 ml water administered according to serum glucose concentrations) or to angioplasty without GIK. Although the mortality reduction in the overall population did not reach significance, the results showed that in 856 patients without signs of heart failure (i.e. Killip class I) the mortality reduction was 3.0% ( $P=0.01$ ).

### Conclusion

It is to be expected that in the future the role of GIK, with or without meticulous glucose regulation, will be established in the treatment of various conditions [14]. At present clinical studies only support its effectiveness in patients admitted to a surgical intensive care unit and treated with meticulous glucose regulation combined with nutrition, and in patients with diabetes mellitus and acute myocardial infarction who are treated with an insulin–glucose infusion and intensive insulin therapy for at least 3 months. New clinical studies will show whether experimentally obtained results, such as the effect of insulin on immune function and apoptosis [15], can effectively be translated into routine practice, particularly in sepsis, septic shock and burns patients.

### Competing interests

None declared.

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